Bioactive components from garlic on brain resiliency against neuroinflammation and neurodegeneration (Review)

HAILONG SONG[1], JIANKUN CUI[1,2], VALERI V. MOSSINE[3],
C. MICHAEL GREENLIEF[4], KEVIN FRITSCHE[5], GRACE Y. SUN[1,3] and ZEZONG GU[1,2]

[1]Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine,
Columbia, MO 65212; [2]Truman VA Hospital Research Service, Columbia, MO 65201; [3]Department of Biochemistry,
University of Missouri School of Medicine, Columbia, MO 65212; [4]Department of Chemistry, and
[5]Division of Animal Sciences, University of Missouri, Columbia, MO 65211, USA

Abstract. Garlic (*Allium sativum*) has been widely used for culinary and medicinal purposes. Aged garlic extract (AGE) and sulfur-containing compounds, including S-allylcysteine (SAC) are well documented botanical active components of garlic. AGE is prepared by the prolonged extraction of fresh garlic with aqueous ethanol and is considered a nutritional supplement with potential to promote human health. SAC is a water-soluble organosulfur compound and the most abundant component of AGE. Studies have demonstrated that both AGE and SAC can exert neuroprotective effects against neuroinflammation and neurodegeneration. Another bioactive component in AGE is N-α-(1-deoxy-D-fructos-1-yl)-L-arginine (FruArg) although less is known about the metabolic activity of this compound. The main aim of this review was to provide an undated overview of the neuroprotective perspectives of these active garlic components (AGE, SAC and FruArg). Of interest, our studies and those of others indicate that both AGE and FruArg are involved in the regulation of gene transcription and protein expression. AGE has been shown to reverse 67% of the transcriptome alteration induced by endotoxins-lipopolysaccharide (LPS), and FruArg has been shown to account for the protective effects by reversing 55% of genes altered in a cell-based neuroinflammation paradigm stimulated by LPS in murine BV-2 microglial cells. AGE and FruArg can alleviate neuroinflammatory responses through a variety of signaling pathways, such as Toll-like receptor and interleukin (IL)-6 signaling, as well as by upregulating the nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated oxidative stress pathways known to promote microglial resiliency against neuroinflammation and neurodegeneration. The capability of FruArg to pass through the blood-brain barrier further supports its potential as a therapeutic compound. In summary, these experimental results provide new insight into the understanding of the neuroprotective effects of garlic components in promoting brain resiliency for health benefits.

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1. Introduction

Garlic (*Allium sativum L.*) is well-recognized as a botanical resource for health maintenance, largely due to its active components with antioxidant properties (1). However, fresh garlic causes indigestion and its odor is a possible social deterrent (2). Fresh garlic soaked in 15-20% aqueous ethanol for >10 months at room temperature produces aged garlic extract (AGE), which is odorless and contains rich antioxidant chemicals that prevent oxidative damage (3,4). It has been demonstrated that AGE can reduce oxidative damage by scavenging reactive oxygen species (ROS) and inhibiting the formation of lipid peroxides (5). In addition, there is evidence to indicate that AGE can reduce the risk of cardiovascular and cerebrovascular diseases, and possibly inhibit carcinogenesis (6-12). One of the major bioactive components in AGE is S-allylcysteine (SAC), a stable organosulfur compound with a thiol group (13). SAC also possesses antioxidant properties and can neutralize excessive electrophilic species (14).

Apart from SAC, AGE also contains a carbohydrate derivative, N-α-(1-deoxy-D-fructos-1-yl)-L-arginine (FruArg). FruArg

is an Amadori rearrangement product from the amino-carbonyl (Maillard) reaction of AGE, which is a non-enzymatic browning reaction occurring between amino acids and sugars (15,16). FruArg was first isolated from the non-saponin fraction of Korean red ginseng, as a principle antioxidant species with potent effects on lowering blood pressure and improving micro-circulation (17,18). The antioxidant potential of FruArg has been demonstrated in an *in vitro* model of atherosclerosis (19), where FruArg was shown to efficiently block copper(II)-induced low density lipoprotein (LDL) oxidation. Moreover, was demon-strated FruArg that inhibited, in a dose-dependent manner, the release of peroxides by macrophages exposed to oxidized LDL (19). Such activities are attributed to the metal-chelating and peroxide-scavenging capabilities of FruArg. Previous studies by our group also demonstrated the ability of both AGE and FruArg to reduce nitric oxide (NO) production in lipopoly-saccharide (LPS)-stimulated murine microglial BV-2 cells in a concentration-dependent manner (20,21). Subsequently, we applied quantitative proteomic analysis by two-dimensional differential in-gel electrophoresis (2D-DIGE) integrated with liquid chromatography tandem mass spectrometry (LC-MS/MS) to profile the proteome patterns and to determine the effects of AGE and FruArg on LPS-stimulated BV-2 cells (20). Furthermore, we investigated gene regulation and associated signaling pathways using the RNA-sequencing (RNA-Seq) approach coupled with machine learning based bioinformatics analysis (21). Importantly, in another study on mice using the sensitive ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) protocol, we obtained evidence that FruArg can pass through the blood-brain barrier in mice (22). The ability of FruArg to penetrate the blood-brain barrier in subnanomolar concentrations suggests its potential to be studied as a therapeutic compound.

Currently, over 340 publications from PubMed are related to studies on AGE. SAC has also been explored in numerous research articles (approximately 270). However, there are currently only 9 studies available on FruArg (Fig. 1), at least to the best of our knowledge. In this review, we summarize the neuroprotective effects of garlic bioactive components, including AGE, SAC and FruArg, respectively, in three sepa-rate sections.

2. Neuroprotective effects of AGE

AGE is commercially available and has been widely used in studies investigating its beneficial effects on health (3,19,23). Emerging evidence suggests that AGE attenuates the oxidative damage and neuroinflammation underlying a variety of neuro-logical diseases, such as Alzheimer's disease (AD) as well as other age-related neurodegenerative disorders (14). In earlier studies, AGE was found to protect against cellular damage occurring due to the toxic effects of β-amyloid peptide (Aβ) *in vitro* (24,25). Another study also demonstrated the suppres-sive effects of AGE on both the Aβ load and the numbers of Aβ plaques in the brains of amyloid precursor protein (APP) transgenic (Tg) mice as compared to untreated Tg mice used as controls (26). Mechanistically, AGE can inhibit caspase-3 activation, and can counteract the toxicity of Aβ (27,28). Additionally, in relation to the pathogenesis of AD, AGE can reduce tau hyperphosphorylation with a decreased activity of
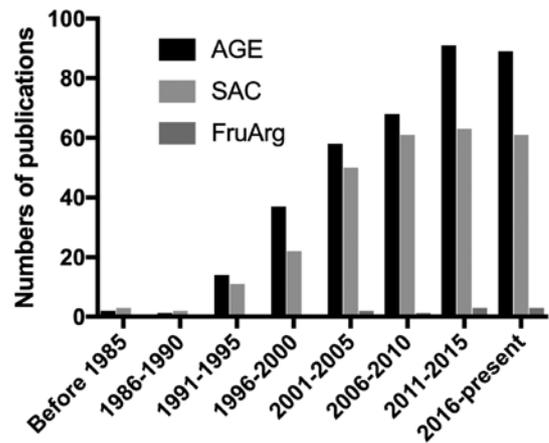

Figure 1. Literature search on 'aged garlic extract (AGE)', 'S-allylcysteine (SAC)' and '*N*-α-(1-deoxy-D-fructos-1-yl)-L-arginine (FruArg)' from PubMed dated on March 20, 2019.

glycogen synthase kinase (GSK)-3β (26). Furthermore, the neuroprotective effects of AGE on related cognitive dysfunc-tion have also been explored. The oral administration of AGE has been shown to improve spatial recognition memory in cognitively impaired rats induced by Aβ42. The increased expression of synaptic proteins may underlie the improved cognitive functions (29). This effect was also accompanied by the attenuation of the loss of cholinergic neurons and neuroin-flammation via the suppression of microglial activation and the secretion of interleukin (IL)-1β (30,31). Neuroinflammation plays an important role in the pathogenesis of a number of neurodegenerative disorders (32,33).

Microglial cells are the resident immune cells in the central nervous system (CNS). After being exposed to brain injuries, stress or infections, microglial cells are the first line of defense that are capable of conferring resilience against oxidative stress and neuroinflammatory responses. Moreover, microglial cells can also become activated and release inflam-matory mediators, such as ligands of Toll-like receptors (TLRs), IL-1β, tumor necrosis factor-α (TNF-α), reactive oxygen species (ROS) and NO (34,35). A number of botanical compounds with antioxidant properties have been explored to target neuroinflammation. There is evidence to indicate that AGE can exert potent neuroprotective effects via the ameliora-tion of pro-inflammatory responses (36,37).

The effects of AGE on neuroinflammation and oxida-tive stress have been extensively investigated (38). AGE can reduce the activation of microglia and astrocytes [by immune-detection of the respective ionized calcium-binding adapter molecule 1 (Iba1) and Glial fibrillary acidic protein (GFAP) expression levels], and can thus mitigate neuroin-flammatory responses (13,39). Additionally, AGE can reduce the expression levels of neuroinflammatory mediators, including IL-1β, nuclear factor (NF)-κB, TLR4, nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1) in microglial and endothelial cells and/or Aβ-induced neuroinflammation in rats (21,30,40). AGE has also been found to alleviate oxidative stress by scavenging ROS, inhib-iting LDL oxidation, enhancing antioxidant signaling [such as superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione (GSH)] and mitigating lipid peroxidation
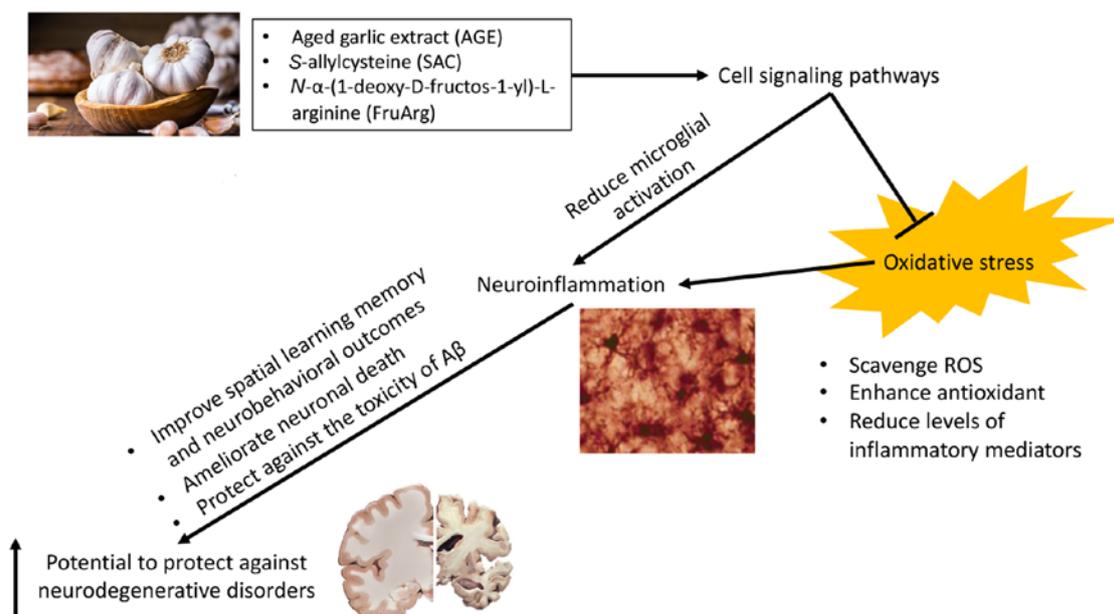
Figure 2. Schematic diagram depicting the neuroprotective effects of garlic components on oxidative stress, neuroinflammation and neurodegeneration. ROS, reactive oxygen species; RNS, reactive nitrogen species; Aβ, β amyloid; BBB, blood-brain barrier.

[malondialdehyde (MDA)] (41-45). Our previous study also demonstrated the protective effects of AGE on ROS and NO production from L-arginine by NO synthase (NOS) (20). Excessive NO can undergo oxidative-reductive reactions and cause cellular damage by endangering reactive nitrogen species (RNS) (46). Nitrosative stress elicited by NO and RNS has been implicated in the pathogenesis of neurodegenerative diseases, such as AD, Parkinson's disease and traumatic brain injury (TBI) (47-52). Previous studies by our group demonstrated that AGE can attenuate NO production in microglial BV-2 cells (20,21). Specifically, treatment with AGE (0.1-1%) or FruArg (2-5 mM) for 20 h was found to significantly reduce NO production in a dose-dependent manner in BV2 cells against LPS-induced neuroinflammation (20). Additionally, AGE was found to be capable of regulating both marker protein and gene expression levels, such as caspase-3, IL-6, NF-κB, HO-1, SOD2 and peroxiredoxin-1 (PRDX1), against LPS-induced neuroinflammation (21). By using quantitative proteomics and RNA-Seq analysis, it is possible to unbiasedly identify key canonical pathways associated with LPS stimulation, including TLR signaling, IL-6 signaling, IL-10 signaling, tumor necrosis factor receptor 2 (TNRF2) signaling, 14-3-3-mediated signaling, superoxide radical degradation, pentose phosphate pathway (oxidative branch) and Nrf2-mediated oxidative stress response through AGE treatment (20,21). Our findings are consistent with those of others demonstrating that AGE is capable of reducing the oxidative-nitrosative stress, alleviating neuroinflammation and exerting neuroprotective effects against the pathogenesis of neurodegenerative diseases (37).

3. Neuroprotective effects of SAC: A major active component of AGE

SAC is formed by the catabolism of γ-glutamyl-S-allylcysteine. The antioxidant effects of SAC in the nervous system have

been reported (53). Indeed, numerous neuroprotective effects of AGE mentioned above are derived from its multipotent phytochemicals, of which SAC is a major component. The amount of bioactive SAC from AGE increases during the aging process of the garlic, and SAC plays important roles as an antioxidant (37). SAC has been found to destabilize Aβ fibrils *in vitro* (54). Aβ-induced hippocampal neurodegeneration and neuronal cell death can be prevented by SAC treatment, which is mediated through the caspase-12-dependent pathway and SAC can attenuate endoplasmic reticulum stress (41). SAC can also inhibit apoptosis by regulating caspase-3 activity via phosphoinositide-3-kinase (PI3K), protein kinase B (PKB/Akt) and c-Jun N-terminal kinase (JNK) signaling (41,53). Research has also indicated that SAC can protect against 1-methyl-4-phenylpyridinium (MPP) toxicity associated with reduced lipid peroxidation and superoxide radical production. As a result, SAC is able to improve the MPP-induced locomotor impairment in a mouse model of Parkinson's disease (PD) (55). Researchers have shown the protective effects of SAC on other neurobehavioral outcomes. The oral administration of SAC has been shown to protect against LPS-induced cognitive deficits in rats, and to improve spatial recognition memory in the Y-maze, the discrimination ratio in the novel object discrimination task, and the retention and recall in the passive avoidance test (13). SAC has been shown to alleviate the spatial recognition memory and cognitive deficits associated with novelty recognition and passive avoidance in rats (56). These studies identified the reducing effects of SAC on acetylcholinesterase activity, the lipid peroxidation marker, MDA, as well as its promoting effects on the levels of antioxidant system markers, including SOD, catalase and reduced GSH in the hippocampal brain subregion. Data have also demonstrated that SAC can modulate NF-κB, TLR-4 and TNF-α, and prevent the reduction of Nrf2 and HO-1 (13,56,57). Due to its anti-inflammatory properties, a recent study used SAC for the treatment of

experimental autoimmune encephalomyelitis in mice. That study demonstrated that SAC not only regulated TNF-α, IL-17 and matrix metalloprotease 9 levels, but was also capable of attenuating inflammatory cell infiltration, axonal demyelination and axonal loss in the lumbar spinal cord (58). Additionally, another study used allyl sulfide in aging mice and demonstrated that it ameliorated gut dysbiosis and memory functions associated with lncRNA-Hotair regulation and H3K27ac regulatory activity (59). Taken together, these neuroprotective effects, namely the reduction of oxidative stress and inflammatory responses may be the key underlying benefits for SAC against neurodegeneration.

4. FruArg: A potential alternative compound with which to mitigate neuroinflammation

FruArg, also known as fructosyl arginine, is fractioned from AGE as a bioactive compound and can be chemically synthesized (23). FruArg is identified in AGE at a concentration range of 2.1-2.4 mmol/l. The antioxidant activity of FruArg is as potent as that of ascorbic acid, considering its hydrogen peroxide scavenging activity (23,42). FruArg was first studied, along with AGE and SAC, in the treatment of sickle cell anemia by inhibiting the formation of dense cells *in vitro* (60). Since the year 2000, researchers have indicated the anti-tumor effects of FruArg through its ability to inhibit cancer cell proliferation and adhesion (61). However, there is limited information available regarding the neuroprotective effects of FruArg. Therefore, to the best of our knowledge, we were the first to have studied the effects of FruArg on LPS-induced inflammatory responses in BV2 microglial cells (14,20,21). Our previous studies demonstrated that FruArg reduced LPS-induced NO production in a concentration-dependent manner (20,21). The ability of FruArg to mitigate neuroinflammation was investigated using quantitative proteomics and RNA-Seq analysis. We demonstrated that FruArg alleviated oxidative stress and neuroinflammatory responses with similar potency as AGE. In fact, both AGE and FruArg shared a large number of regulated protein and gene markers, with distinct profiles in those differentially expressed targets by bioinformatics analyses of the differential levels of the targets in their proteomes and transcriptomes, respectively, affecting the scales of the signaling pathways. Consistently, FruArg was found to alter the Nrf2-mediated oxidative stress response, 14-3-3-mediated signaling, superoxide radical degradation, glutathione biosynthesis, TLR, IL-10, TNRF2 and IL-6 signaling pathways. Of note, several signaling pathways on protein and gene levels regulated by FruArg were also shared with AGE treatment, supporting that FruArg contributed to certain anti-inflammatory effects of AGE. Additionally, we also identified that FruArg treatment triggered the protein-protein interactions associated with immunological disease, and cellular assembly and organization, cellular movement, cell death and survival and cell morphology (20,21).

Apart from an *in vitro* analysis showing the anti-inflammatory potential of FruArg, researchers have also examined whether FruArg can be delivered to the brain for the treatment of neurological disorders. The blood-brain barrier is known to block >98% of all small molecular drug candidates entering the brain, thus causing a major issue for drug therapy development (62). Therefore, it is critical that we previously demonstrated that FruArg could pass through the blood-brain barrier in subnanomolar concentrations in mice (22). Using the UPLC-MS/MS detection protocol, the results demonstrated that, in spite of being highly hydrophilic, FruArg could be absorbed and appear in the blood circulation following an intraperitoneal injection. The pharmacokinetics analysis determined the elimination rate in plasma samples (fraction of FruArg that is removed from the body per unit time) was 6.91×10^{-2}/min, with a half-life (t1/2) of 10.03 min, clearance (Cl) of 1.8×10^{-4} l·min, and volume distribution (VD) of 2.63×10^{-3} l. Ongoing studies by our research group aim to utilize ribosome profiling (Ribo-Seq) technology by profiling the mRNA activation to analyze such neuroprotective effects of FruArg in the same *in vitro* model. This could help us to provide a systematic and quantitative method, data profiling and visualization to further elucidate the molecular and genetic mechanisms of the neuroprotective effects of FruArg. Considering that our studies have provided a basis for the anti-inflammatory properties of FruArg, future studies are warranted to include in-depth investigations to examine the mechanisms whereby FruArg can exert its neuroprotective effects, for the prevention and treatment of neurological disorders.

5. Conclusions

In conclusion, the neuroprotective effects of garlic components, including AGE, SAC and FruArg on oxidative stress, neuroinflammation and neurodegeneration were discussed herein (Fig. 2). The health benefits of AGE, SAC and FruArg are supported by extensive research on various experimental paradigms. Of importance, our studies demonstrated that FruArg mitigates LPS-induced neuroinflammatory responses and that it is capable of penetrating the blood-brain barrier. This constitutes important information which can provide a promising basis and may open new avenues for promoting brain resilience for health maintenance against neuroinflammation and neurodegeneration from neurological disorders.

Availability of data and materials

Not applicable.

Authors' contributions

HS, JC and ZG wrote the manuscript with significant scientific contributions and concept inputs from VVM, CMG, KF and GYS. All authors have reviewed and approved the current version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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